

Expanding spectrum of immune checkpoint inhibitor–associated cardiovascular toxicity: beyond myocarditis

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Abstract

Immune checkpoint inhibitors (ICIs) have transformed the treatment of multiple malignancies but are increasingly recognized as a cause of cardiovascular toxicity. Although ICI-associated myocarditis has traditionally received the greatest attention because of its potentially fulminant course and high risk of adverse outcomes, accumulating evidence indicates that the cardiovascular effects of checkpoint inhibition extend substantially beyond myocarditis. The expanding clinical spectrum includes accelerated atherosclerosis and acute coronary syndromes, pericardial disease, arrhythmias and conduction disturbances, heart failure and non-inflammatory ventricular dysfunction, as well as vascular and thromboembolic complications. These manifestations appear to arise through heterogeneous mechanisms, including disruption of myocardial immune tolerance, T-cell-mediated tissue injury, endothelial activation, vascular inflammation, and acceleration or destabilization of pre-existing cardiovascular disease. This broader spectrum creates important diagnostic challenges because cardiovascular events occurring during ICI therapy may reflect direct immune-mediated toxicity, progression of underlying cardiovascular disease, cancer-associated complications, or effects of concomitant therapies. Accordingly, cardiovascular assessment should extend beyond surveillance for myocarditis and incorporate baseline risk characterization, optimization of modifiable cardiovascular risk factors, and phenotype-directed use of biomarkers and multimodality imaging. Management should similarly be tailored to the specific cardiovascular phenotype and severity, balancing prompt treatment of potentially life-threatening immune-mediated toxicity against unnecessary interruption of effective anticancer therapy. Emerging biomarkers, clonal hematopoiesis, advanced cardiovascular imaging, immune profiling, and multi-omics approaches may enable more individualized risk prediction in the future. This review summarizes the mechanisms, clinical manifestations, diagnosis, surveillance, and management of the expanding spectrum of ICI-associated cardiovascular toxicity, with particular emphasis on cardiovascular complications beyond myocarditis.

Keywords: immune checkpoint inhibitors, cardiovascular toxicity, cardio-oncology, myocarditis, atherosclerosis, immune-related adverse events

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Introduction

Immune checkpoint inhibitors (ICIs) have fundamentally changed the therapeutic landscape of oncology by restoring antitumor immune responses through blockade of inhibitory immune checkpoints. Antibodies targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) have demonstrated durable clinical benefit across a broad and continually expanding range of malignancies.¹ However, enhancement of antitumor immunity may disrupt peripheral immune tolerance and result in immune-related adverse events (irAEs) affecting virtually any organ system, including the cardiovascular system.^{1,2}

Cardiovascular toxicity related to ICIs initially attracted attention because of myocarditis, a relatively uncommon but potentially life-threatening complication. Early reports described fulminant myocarditis characterized by myocardial T-cell infiltration, electrical instability, and rapid clinical deterioration, particularly in patients receiving combination checkpoint blockade.² Subsequent pharmacovigilance data confirmed the strong association between ICI exposure and myocarditis and also identified other inflammatory

cardiovascular toxicities, including pericardial disease and vasculitis.³ Consequently, myocarditis has historically dominated both clinical concern and research regarding ICI-associated cardiovascular toxicity.

Accumulating evidence, however, indicates that the cardiovascular effects of ICIs extend substantially beyond myocarditis. Reported manifestations now encompass accelerated atherosclerosis and acute coronary syndromes, pericardial disease, arrhythmias and conduction disturbances, stress cardiomyopathy, non-inflammatory left ventricular dysfunction, heart failure, and vascular complications.⁴⁻⁶ Importantly, some of these events may represent acceleration of pre-existing cardiovascular disease rather than conventional acute immune-mediated organ toxicity. For example, ICI exposure has been associated with increased atherosclerotic cardiovascular events and accelerated progression of atherosclerotic plaque.⁴ The most recent International Cardio-Oncology Society position statement therefore emphasizes a broader conceptual framework for ICI-associated cardiovascular toxicity that extends beyond myocarditis alone.⁵

This review summarizes the expanding spectrum of ICI-associated cardiovascular toxicity, with particular emphasis on non-myocarditis manifestations, their underlying mechanisms, clinical recognition,

surveillance, and management. It also discusses emerging approaches to cardiovascular risk stratification and the challenge of balancing cardiovascular safety with preservation of effective anticancer therapy.

Biological basis of ICI-associated cardiovascular toxicity

The cardiovascular toxicity of immune checkpoint inhibitors is closely linked to the physiological role of immune checkpoints in maintaining self-tolerance and limiting inappropriate immune activation within cardiovascular tissues. Under normal conditions, inhibitory pathways such as PD-1/PD-L1 and CTLA-4 restrain T-cell activation and protect against excessive immune-mediated tissue injury. Although blockade of these pathways enhances antitumor immunity, the same mechanism may disrupt cardiovascular immune homeostasis and facilitate immune responses against myocardial, vascular, and other cardiovascular structures.^{7,8}

Among these pathways, PD-1/PD-L1 signaling appears particularly important in maintaining myocardial immune tolerance. Experimental evidence indicates that disruption of PD-1 signaling can increase susceptibility to autoimmune myocardial injury, while PD-L1 expression within cardiac tissue may serve as an adaptive protective mechanism during inflammatory stress.⁷ CTLA-4 acts predominantly by limiting T-cell activation and proliferation, and its inhibition similarly shifts the immune balance toward a more activated phenotype. Simultaneous blockade of CTLA-4 and PD-1 may therefore produce more profound loss of immune restraint, providing a biological explanation for the greater cardiovascular toxicity observed with combination ICI therapy.^{2,7}

The pathogenesis of ICI-associated myocarditis involves both systemic immune activation and local myocardial immune responses. Histopathological and translational studies demonstrate myocardial infiltration predominantly by activated T lymphocytes and macrophages.^{2,7} An important proposed mechanism is the expansion of T-cell clones capable of recognizing antigens shared between tumor cells and cardiomyocytes. Such cross-reactivity may redirect an effective antitumor immune response toward cardiac tissue. Additional mechanisms include cardiac-specific antigen recognition, altered interactions between T cells and macrophages, and amplification of inflammatory signaling through cytokines and chemokines.^{7,9} These observations suggest that ICI-associated myocardial injury is not attributable to a single pathway but rather results from disruption of several interconnected mechanisms of peripheral and tissue-specific immune tolerance.

Importantly, immune checkpoint signaling also has a physiological role within the vascular system. Atherosclerosis is itself an immune-mediated inflammatory disease in which T-cell activation contributes to plaque development and instability. PD-1/PD-L1 and CTLA-4

signaling normally exert inhibitory effects on vascular inflammation, and therapeutic blockade of these pathways may remove this protective restraint.^{8,10} Preclinical studies have demonstrated that checkpoint inhibition increases effector CD4+ and cytotoxic CD8+ T-cell accumulation within atherosclerotic plaques, enhances endothelial activation, and promotes a more inflammatory plaque phenotype with enlargement of the necrotic core.¹⁰ These mechanisms provide biological support for clinical observations linking ICI exposure to accelerated atherosclerotic plaque progression and increased cardiovascular events.⁴ Thus, vascular toxicity may represent chronic dysregulation of a pre-existing inflammatory process rather than an acute organ-specific irAE analogous to myocarditis.

Endothelial activation may provide an additional link between immune activation and vascular complications. Increased expression of adhesion molecules facilitates leukocyte recruitment into the arterial wall, while activated T cells and pro-inflammatory cytokine signaling can promote endothelial dysfunction and plaque inflammation.^{9,10} The resulting vascular environment may contribute not only to accelerated atherosclerosis but potentially also to vasculitis and thrombotic complications. However, separating direct ICI-mediated vascular injury from the effects of malignancy, conventional cardiovascular risk factors, and concomitant anticancer therapies remains challenging.

Host-specific inflammatory susceptibility may further modify cardiovascular risk. Clonal hematopoiesis of indeterminate potential (CHIP), an age-related expansion of hematopoietic clones carrying somatic mutations, has emerged as a potential link between cancer, inflammation, and cardiovascular disease. In a prospective cardio-oncology cohort, CHIP was independently associated with an increased risk of ICI-associated myocarditis, although the relatively small sample size requires cautious interpretation and validation in larger populations.¹¹ This observation raises the possibility that pre-existing alterations in immune and hematopoietic biology may determine why cardiovascular toxicity develops in only a subset of ICI-treated patients.

Collectively, these findings support a broader biological model of ICI-associated cardiovascular toxicity. Checkpoint inhibition can disrupt myocardial immune tolerance, enhance T-cell–mediated tissue injury, activate vascular inflammation, and potentially accelerate pre-existing cardiovascular disease. The clinical phenotype that ultimately develops may therefore depend on the interaction among the specific checkpoint pathway inhibited, intensity of immune activation, combination therapy, underlying cardiovascular substrate, and individual inflammatory susceptibility. This mechanistic heterogeneity provides a biological basis for the expanding clinical spectrum of ICI-associated cardiovascular toxicity beyond myocarditis. An integrated overview of the proposed mechanisms, expanding cardiovascular spectrum, risk assessment, and phenotype-directed management of ICI-associated cardiovascular toxicity is presented in Figure 1.

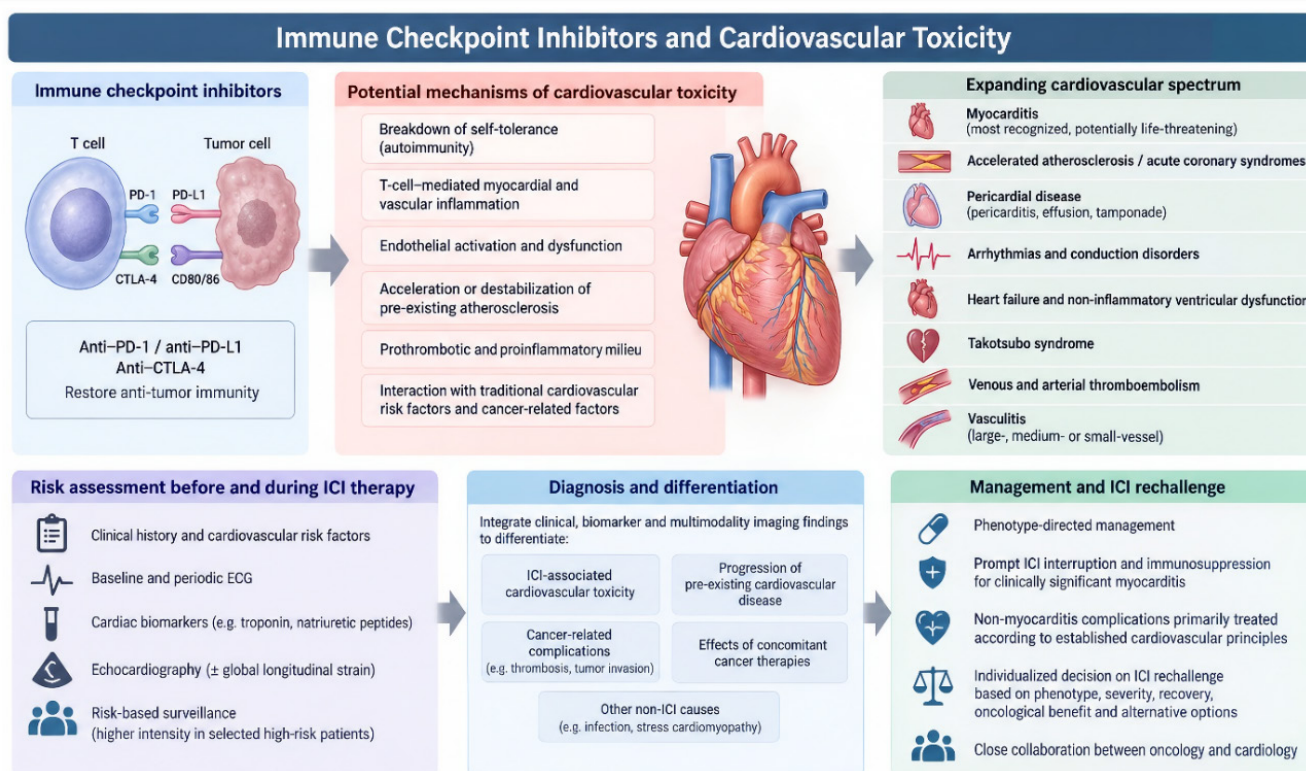


Figure 1 Immune checkpoint blockade may disrupt cardiovascular immune tolerance and promote myocardial and vascular inflammation, endothelial dysfunction, accelerated atherosclerosis, and thromboembolic complications. Cardiovascular manifestations extend beyond myocarditis and include acute coronary syndromes, pericardial disease, arrhythmias and conduction disorders, heart failure, Takotsubo syndrome, thromboembolism, and vasculitis. Risk-based surveillance and phenotype-directed diagnostic and therapeutic strategies are essential to distinguish ICI-associated toxicity from pre-existing cardiovascular disease and other cancer-related complications and to guide decisions regarding ICI interruption or rechallenge. (Abbreviation: ICI, immune checkpoint inhibitor).

Myocarditis: the prototype cardiovascular immune-related adverse event

ICI-associated myocarditis is the most extensively characterized cardiovascular immune-related adverse event and remains the prototype against which other ICI-related cardiovascular toxicities are often considered. Although uncommon, its clinical importance derives from its potentially fulminant course and high risk of major cardiovascular complications. Early pharmacovigilance and registry studies estimated an incidence of approximately 0.5–1%, although reported rates vary according to the population studied, diagnostic criteria, surveillance strategy, and ICI regimen.^{3,12} Combination checkpoint blockade, particularly concurrent inhibition of CTLA-4 and PD-1/PD-L1 pathways, is consistently associated with greater risk than ICI monotherapy.^{2,12} Myocarditis typically occurs early after treatment initiation. In a multicenter registry, the median time from the first ICI exposure to myocarditis onset was 34 days, with most cases occurring within the first few months of therapy.¹²

Clinical presentation is heterogeneous, ranging from asymptomatic biomarker elevation to chest pain, dyspnea, heart failure, ventricular arrhythmias, high-grade atrioventricular block, cardiogenic shock, and sudden cardiac death.^{5,12} Importantly, preserved left ventricular ejection fraction does not exclude clinically significant disease. In the initial multicenter registry, 38% of major adverse cardiovascular events occurred in patients with a normal ejection fraction.¹² ICI myocarditis may also coexist with other immune-related toxicities, particularly myositis and myasthenia gravis, creating a clinically important overlap syndrome associated with severe disease.^{5,7}

Diagnosis requires integration of clinical presentation, biomarkers, electrocardiography, multimodality imaging, and, when necessary, endomyocardial biopsy. Cardiac troponin is central to the diagnostic evaluation and provides prognostic information, while natriuretic peptides may support the assessment of myocardial dysfunction.^{5,12} Interpretation of troponin requires particular caution in patients with concomitant ICI-related myositis, because cardiac troponin T may be elevated in the setting of skeletal muscle inflammation; cardiac troponin I may provide greater cardiac specificity in this context.⁵ Electrocardiographic abnormalities are frequent and may include conduction disturbances, ST–T changes, atrial or ventricular arrhythmias, and QRS prolongation. In an international registry, QRS duration increased significantly at myocarditis presentation and greater QRS prolongation was associated with an increased risk of major adverse cardiovascular events.¹³

Transthoracic echocardiography remains an important first-line imaging modality but has limited sensitivity when used in isolation. A normal LVEF cannot exclude myocarditis, and assessment of global longitudinal strain may identify myocardial dysfunction despite preserved systolic function.⁵ Cardiac magnetic resonance (CMR) provides complementary tissue characterization and plays a major role in the diagnostic pathway. However, conventional CMR findings may be less sensitive than in other forms of acute myocarditis. In an international registry of 103 patients undergoing CMR for ICI-associated myocarditis, late gadolinium enhancement was present in only 48%, and 61% of patients had preserved LVEF.¹⁴ Consequently, a negative or nondiagnostic CMR should not be used alone to exclude ICI-associated myocarditis when clinical suspicion

remains high. Endomyocardial biopsy remains particularly valuable in diagnostically uncertain or severe cases and can demonstrate the characteristic lymphocytic and macrophage-predominant inflammatory infiltrate.^{2,5,15}

Several diagnostic frameworks have been proposed to standardize case definitions. The Bonaca criteria categorize suspected cases according to pathological and clinical evidence, whereas subsequent IC-OS definitions incorporated troponin elevation together with major and minor clinical criteria.^{15,16} Contemporary recommendations emphasize exclusion of alternative diagnoses, particularly acute coronary syndrome, infectious myocarditis, and other causes of myocardial injury.⁵

Once ICI-associated myocarditis is suspected, ICI therapy should generally be withheld and diagnostic evaluation initiated promptly. In clinically significant cases, early high-dose corticosteroid therapy is the cornerstone of treatment.⁵ Observational evidence suggests that both timing and initial corticosteroid dose influence outcome. In a multicenter cohort, earlier administration and higher initial doses of corticosteroids were associated with a lower incidence of major adverse cardiovascular events.¹⁷ Patients with hemodynamic instability, malignant arrhythmias, advanced conduction disease, or inadequate response to corticosteroids may require intensified immunosuppression and advanced cardiovascular supportive care. Refractory cases have been treated with several immunomodulatory strategies, including abatacept and other targeted agents, although robust randomized evidence remains limited.⁵

Despite its relatively low incidence, myocarditis illustrates the fundamental consequences of disrupting cardiovascular immune

tolerance during checkpoint inhibition. Nevertheless, focusing exclusively on myocarditis provides an incomplete representation of ICI cardiovascular toxicity. Increasing evidence indicates that ICIs can affect the coronary arteries, pericardium, cardiac conduction system, ventricular function, and vascular system through mechanisms that are not necessarily accompanied by overt myocardial inflammation. Recognition of these non-myocarditis phenotypes is therefore essential to understanding the full cardiovascular impact of contemporary ICI therapy.

The expanding cardiovascular spectrum beyond myocarditis

Although myocarditis remains the most recognized and potentially devastating cardiovascular irAE associated with ICIs, it represents only one component of a substantially broader spectrum of cardiovascular toxicity. Increasing clinical and translational evidence indicates that checkpoint inhibition may affect the coronary circulation, pericardium, cardiac electrical system, ventricular function, and vascular system.^{3,5,18} Importantly, these complications are mechanistically heterogeneous. Some appear to represent direct immune-mediated tissue injury, whereas others may result from acceleration of pre-existing inflammatory cardiovascular disease or interaction between cancer-related and treatment-related risk factors. The major clinical manifestations, diagnostic approaches, and general management principles across the spectrum of ICI-associated cardiovascular toxicity are summarized in Table 1.

Table 1 Clinical spectrum of ICI-associated cardiovascular toxicity

Cardiovascular toxicity	Main manifestations	Key diagnostic tools	General management
Myocarditis	Chest pain, HF, VA, AV block, shock	cTn, ECG, TTE/GLS, CMR ± EMB	Hold ICI; high-dose corticosteroids; escalation if refractory
Atherosclerosis / ACS	Angina, MI, ischemic stroke	ECG, cTn, coronary/vascular imaging	Standard ACS therapy; revascularization; CV risk reduction
Pericardial disease	Pericarditis, effusion, tamponade	ECG, TTE, CT/CMR	Anti-inflammatory therapy; drainage if tamponade
Arrhythmias / conduction disease	AF, SVT, VA, AV block	ECG, rhythm monitoring, TTE	Rhythm-specific therapy; exclude myocarditis/ischemia
LV dysfunction / HF	Dyspnea, edema, reduced exercise capacity	TTE/GLS, NP, CMR when indicated	Guideline-directed HF therapy; exclude myocarditis
Takotsubo syndrome	ACS-like presentation, acute LV dysfunction	TTE, coronary imaging, CMR	Supportive therapy; exclude ACS/myocarditis
Thromboembolism	VTE, stroke, arterial thrombosis	Territory-specific imaging	Anticoagulation/standard vascular treatment
Vasculitis	Variable organ-specific ischemic manifestations	Vascular imaging ± biopsy	Hold ICI; immunosuppression when clinically significant

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; AV, atrioventricular; CMR, cardiac magnetic resonance; CT, computed tomography; cTn, cardiac troponin; CV, cardiovascular; ECG, electrocardiogram; EMB, endomyocardial biopsy; GLS, global longitudinal strain; HF, heart failure; ICI, immune checkpoint inhibitor; LV, left ventricular; MI, myocardial infarction; NP, natriuretic peptide; SVT, supraventricular tachycardia; TTE, transthoracic echocardiography; VA, ventricular arrhythmia; VTE, venous thromboembolism.

Accelerated atherosclerosis and acute coronary syndromes

The association between ICI therapy and atherosclerotic cardiovascular disease has emerged as one of the most clinically relevant non-myocarditis manifestations. Immune checkpoints are involved in restraining vascular inflammation, and inhibition of PD-1/PD-L1 and CTLA-4 signaling may enhance T-cell activation

within atherosclerotic plaques.¹⁰ This biological mechanism raises the possibility that ICIs may not simply cause acute immune toxicity but may accelerate an underlying chronic inflammatory cardiovascular process.

Clinical evidence supporting this concept was provided by Drobni et al., who evaluated 2,842 patients treated with ICIs and found an approximately threefold increase in the risk of a composite atherosclerotic cardiovascular event after ICI initiation compared

with the period before treatment. In a case-crossover analysis, the incidence of myocardial infarction, coronary revascularization, and ischemic stroke increased following initiation of ICI therapy. Moreover, a separate imaging cohort demonstrated an increase in the rate of aortic plaque progression after ICI exposure, providing anatomical evidence consistent with accelerated atherosclerosis.⁴ Interestingly, concomitant statin or corticosteroid use was associated with attenuation of plaque progression, although these observational findings cannot establish a protective treatment effect.

The clinical implications extend beyond acute coronary syndrome. Patients receiving ICIs frequently have conventional cardiovascular risk factors, previous exposure to potentially cardiotoxic cancer therapies, and pre-existing subclinical atherosclerosis. Consequently, checkpoint inhibition may act as an inflammatory accelerator in an already vulnerable vascular substrate. Current evidence therefore supports careful assessment and aggressive management of conventional risk factors, including hypertension, dyslipidemia, diabetes, and smoking, particularly in patients with established atherosclerotic cardiovascular disease.⁵ However, prospective evidence supporting routine initiation of statins or other anti-inflammatory strategies specifically to prevent ICI-associated atherosclerotic events remains insufficient.

Acute coronary syndromes occurring during ICI therapy also present a diagnostic challenge because myocardial infarction and ICI-associated myocarditis can produce overlapping symptoms, electrocardiographic abnormalities, and troponin elevation. Coronary evaluation should therefore not be delayed when an ischemic mechanism is clinically plausible. Furthermore, ACS and myocarditis are not necessarily mutually exclusive, and immune-mediated coronary inflammation or plaque destabilization may coexist with myocardial inflammation.⁵

Pericardial disease

Pericardial involvement is another increasingly recognized cardiovascular complication of ICI therapy and may manifest as acute pericarditis, pericardial effusion, or cardiac tamponade. Pharmacovigilance studies initially identified a signal for pericardial disease among ICI-treated patients,³ but subsequent cohort studies have provided stronger evidence for an association.

In a retrospective study including 2,842 ICI-treated patients and 2,699 age- and cancer-type–matched controls, Gong et al. identified 42 pericardial events among patients receiving ICIs. ICI exposure was associated with a more than fourfold increased risk of pericarditis or new or worsening moderate-to-large pericardial effusion compared with non-ICI-treated controls (hazard ratio 4.37, 95% CI 2.09–9.14).¹⁹ These findings indicate that clinically relevant pericardial disease, although substantially less emphasized than myocarditis, should be considered within the spectrum of cardiovascular irAEs.

Diagnosis can be particularly difficult in patients with advanced malignancy. Pericardial effusion may result from direct malignant involvement, infection, radiation, concomitant anticancer therapy, volume overload, or immune-mediated inflammation. Cytological examination of pericardial fluid may therefore be valuable when malignant involvement is suspected, although malignant cells do not necessarily exclude a concomitant immune-mediated process. Recent systematic evidence also demonstrates that cardiac tamponade may be a frequent presentation among reported severe cases, emphasizing the potential clinical seriousness of this complication.²⁰

Management depends on clinical severity. Hemodynamically significant effusion or tamponade requires urgent drainage according

to standard cardiovascular principles. For clinically significant suspected immune-mediated pericarditis, interruption of ICI therapy and corticosteroid treatment may be required, whereas NSAIDs and colchicine may have a role in less severe presentations.^{5,20} Evidence regarding ICI rechallenge remains limited and should be individualized according to severity, oncological benefit, response to treatment, and availability of alternative cancer therapies.

Arrhythmias and conduction disorders

Atrial and ventricular arrhythmias as well as conduction abnormalities have been reported across the spectrum of ICI-associated cardiovascular toxicity.^{3,5} These manifestations require careful interpretation because they may arise through several distinct pathways. Arrhythmias can occur secondary to myocarditis, myocardial ischemia, ventricular dysfunction, systemic inflammation, metabolic disturbances, or other cancer-related factors and therefore should not automatically be classified as primary immune-mediated electrical toxicity.

Conduction disease is particularly important in ICI-associated myocarditis. High-grade atrioventricular block and intraventricular conduction abnormalities may indicate extensive inflammatory involvement of the conduction system and can accompany severe or fulminant disease. Electrocardiographic studies have demonstrated significant changes in QRS duration during ICI myocarditis, with greater QRS prolongation associated with adverse cardiovascular outcomes.¹³ Continuous rhythm monitoring is therefore warranted in patients with suspected myocarditis or clinically important conduction abnormalities.

Atrial fibrillation and other supraventricular arrhythmias are also encountered during ICI therapy, but causal attribution is more difficult because cancer itself, advanced age, infection, systemic inflammation, and other therapies substantially increase arrhythmia risk. Similarly, ventricular tachyarrhythmias may reflect direct myocardial inflammation, ischemia, or structural cardiac disease. Thus, identification of a new arrhythmia during ICI therapy should trigger evaluation for an underlying cardiovascular irAE rather than being regarded as an isolated diagnosis.⁵

Heart failure and non-inflammatory myocardial dysfunction

ICI-associated ventricular dysfunction is not synonymous with myocarditis. Patients may develop reduced LVEF and clinical heart failure without sufficient evidence of active myocardial inflammation.⁵ This distinction is clinically relevant because the pathophysiology, therapeutic approach, and implications for ICI continuation may differ from those of classical myocarditis.

Stress-induced cardiomyopathy, including Takotsubo syndrome, has also been described in association with ICI treatment.⁵ Potential triggers include systemic inflammatory activation, physical and emotional stress related to malignancy, catecholamine excess, and concomitant irAEs. Because Takotsubo syndrome and myocarditis may both present with chest pain, electrocardiographic abnormalities, troponin elevation, and ventricular dysfunction, CMR and coronary imaging may be necessary to differentiate these entities.

When ventricular dysfunction occurs without evidence of myocarditis, guideline-directed heart failure therapy should be initiated when appropriate, while other potential causes—including ischemic heart disease, previous cardiotoxic chemotherapy, radiation exposure, valvular disease, tachyarrhythmia, and cancer-related systemic illness—should be evaluated. Whether ICI therapy itself

directly produces a distinct non-inflammatory cardiomyopathy remains incompletely defined, and this phenotype requires further prospective characterization.⁵

Vascular and thromboembolic complications

Thromboembolic complications represent one of the most difficult cardiovascular outcomes to attribute specifically to ICI therapy because malignancy itself is a major prothrombotic condition. Nevertheless, accumulating observational data suggest that both venous and arterial thrombotic events deserve attention during ICI treatment.

In a cohort of 672 patients receiving ICIs, Moik et al. reported cumulative incidences of venous and arterial thromboembolism of 12.9% and 1.8%, respectively, during follow-up, with VTE associated with substantially increased mortality.²¹ More recent observational data have similarly reported increased rates of venous thrombosis, myocardial infarction, and ischemic stroke among ICI-treated populations compared with population-based expectations.²² However, the magnitude of the ICI-specific contribution remains uncertain because tumor type, disease stage, previous thrombosis, concomitant systemic therapy, immobility, and other cancer-associated factors are major confounders.

Evidence from randomized trials is less consistent. A meta-analysis of 61 randomized trials found no significant increase in VTE with ICIs compared with control regimens but identified an increased risk of arterial thromboembolism.²³ More recent randomized-trial network analyses have also demonstrated heterogeneity according to treatment regimen and have not consistently reproduced an excess risk across all thromboembolic outcomes.²⁴ Therefore, current evidence does not justify considering every thrombotic event during ICI therapy an immune-mediated toxicity.

Mechanistically, systemic immune activation, endothelial dysfunction, inflammatory cytokine signaling, platelet activation, and acceleration of atherosclerosis may contribute to a prothrombotic

environment. Immune-mediated vasculitis represents a distinct but rare vascular irAE and can involve vessels of different sizes.^{3,5} When vasculitis is suspected, diagnostic evaluation should be tailored to the vascular territory involved and may require multimodality vascular imaging and assessment for systemic inflammatory involvement.

Overall, the expanding spectrum of non-myocarditis cardiovascular complications illustrates the complexity of cardiovascular disease during ICI therapy. The central clinical challenge is not merely recognition of individual phenotypes but determination of causality. Cardiovascular events in patients with cancer may represent direct immune toxicity, exacerbation of pre-existing disease, complications of malignancy, effects of previous or concomitant therapies, or combinations of these mechanisms. A phenotype-based approach integrating clinical presentation, biomarkers, imaging, oncological context, and temporal relationship to ICI exposure is therefore preferable to automatically attributing all cardiovascular events to immune-mediated toxicity.

Cardiovascular risk assessment and surveillance

The expanding spectrum of ICI-associated cardiovascular toxicity raises an important practical question regarding how patients should be assessed before treatment and monitored during therapy. Unlike cardiotoxicity associated with several conventional anticancer agents, an optimal surveillance strategy for ICI therapy has not been established through prospective randomized studies. Moreover, the relatively low incidence of myocarditis must be balanced against its potentially severe consequences, while non-myocarditis cardiovascular events may occur through substantially different mechanisms. Accordingly, contemporary recommendations increasingly favor a risk-based rather than uniform intensive surveillance approach.⁵ A practical framework for cardiovascular assessment and surveillance before and during ICI therapy is summarized in Table 2.

Table 2 Cardiovascular assessment and surveillance during ICI therapy

Clinical stage	Suggested assessment	Key action
Before ICI therapy	CV history, risk factors, ECG, cTn	Identify and optimize baseline CV disease
High-risk patients	TTE ± GLS, NP	Consider closer surveillance
Early ICI cycles	Clinical assessment ± ECG/cTn	Detect early myocardial injury
New CV symptoms	ECG, cTn, NP, TTE	Phenotype-directed diagnostic work-up
Suspected myocarditis	Serial cTn/ECG, TTE, CMR ± EMB	Hold ICI; initiate prompt evaluation/treatment
Long-term follow-up	BP, lipids, glucose, CV symptoms	Optimize ASCVD prevention
After CV toxicity	Biomarkers, ECG/imaging as indicated	Multidisciplinary ICI continuation/rechallenge decision

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CMR, cardiac magnetic resonance; cTn, cardiac troponin; CV, cardiovascular; ECG, electrocardiogram; EMB, endomyocardial biopsy; GLS, global longitudinal strain; ICI, immune checkpoint inhibitor; NP, natriuretic peptide; TTE, transthoracic echocardiography.

Before ICI initiation, cardiovascular assessment should focus on identifying pre-existing cardiovascular disease, conventional risk factors, previous exposure to cardiotoxic anticancer therapies, and clinical features that may increase susceptibility to cardiovascular complications. Particular attention should be given to patients with established coronary artery disease, heart failure, cardiomyopathy, clinically relevant arrhythmias or conduction disease, and previous cancer therapy–related cardiac dysfunction. Combination ICI therapy and concomitant or previous exposure to other potentially cardiotoxic treatments should also be considered when estimating risk.⁵ Baseline cardiovascular optimization is particularly relevant because some ICI-associated complications, especially atherosclerotic events and heart

failure, may represent acceleration or destabilization of pre-existing disease rather than de novo immune-mediated injury.

A baseline electrocardiogram and cardiac troponin measurement provide useful reference values, particularly when subsequent symptoms or biomarker abnormalities develop.⁵ Natriuretic peptides may also be considered, especially in patients with known cardiovascular disease or suspected ventricular dysfunction. Baseline transthoracic echocardiography is most informative in patients with pre-existing cardiovascular disease, previous cardiotoxic treatment, abnormal baseline biomarkers or ECG findings, or other features indicating increased cardiovascular risk. In these patients, assessment

of LVEF and, when technically feasible, global longitudinal strain can establish a useful baseline for comparison during treatment.

Surveillance during ICI therapy remains an area of uncertainty. Because ICI-associated myocarditis typically develops early, heightened clinical vigilance is particularly important during the initial treatment cycles.^{5,12} Serial ECG and troponin assessment during this period may facilitate recognition of otherwise clinically silent myocardial injury, especially in higher-risk patients. However, routine biomarker surveillance in all asymptomatic patients has important limitations. Troponin elevations are not specific for ICI myocarditis and may reflect acute coronary syndrome, pulmonary embolism, sepsis, renal dysfunction, tachyarrhythmia, or concomitant skeletal muscle inflammation. Consequently, an isolated biomarker abnormality should not automatically lead to a diagnosis of myocarditis or permanent interruption of effective anticancer therapy.^{5,16}

Any new cardiovascular symptom during ICI therapy should prompt targeted evaluation. Chest pain, unexplained dyspnea, palpitations, syncope, new fatigue, peripheral edema, or hemodynamic instability may represent manifestations of cardiovascular toxicity. Similarly, newly detected troponin elevation, conduction abnormalities, arrhythmias, or ventricular dysfunction warrant assessment for potential ICI-associated cardiovascular disease. The diagnostic pathway should be phenotype-driven: suspected myocarditis may require biomarkers, ECG, echocardiography, CMR, and occasionally endomyocardial biopsy, whereas ischemic symptoms should prompt appropriate coronary evaluation and suspected pericardial or vascular disease should be investigated using modality-specific approaches.⁵

Importantly, surveillance should extend conceptually beyond early myocarditis detection. Patients with established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors may benefit from periodic reassessment and aggressive optimization of blood pressure, lipid levels, glycemic control, smoking status, and other modifiable risk factors. This approach is supported by evidence linking ICI therapy with accelerated atherosclerotic plaque progression and increased cardiovascular events.⁴ Nevertheless, there is currently insufficient evidence to recommend additional pharmacological preventive therapy solely because a patient is receiving an ICI.

A practical surveillance strategy should therefore combine baseline cardiovascular characterization, increased vigilance during the early phase of ICI therapy, and symptom- or abnormality-driven diagnostic escalation. Patients with substantial baseline cardiovascular disease, combination ICI therapy, previous cardiotoxic treatment, or abnormal cardiovascular findings may reasonably undergo closer monitoring, whereas intensive serial imaging in every asymptomatic patient is unlikely to be justified by current evidence. Most importantly, surveillance should facilitate early recognition of clinically meaningful toxicity without generating unnecessary interruption of potentially life-prolonging cancer therapy. Prospective studies are required to determine which biomarkers, monitoring intervals, and risk-stratification strategies provide the greatest clinical benefit.

Management of cardiovascular toxicity

Management of ICI-associated cardiovascular toxicity requires simultaneous consideration of two potentially competing priorities: rapid control of a potentially life-threatening cardiovascular immune-related adverse event and preservation of effective anticancer therapy whenever feasible. The therapeutic approach should therefore be guided by the specific cardiovascular phenotype and its severity rather than by ICI exposure alone. While myocarditis generally requires immediate interruption of ICI therapy and immunosuppression, other

manifestations, such as atherosclerotic events, arrhythmias unrelated to myocardial inflammation, or thromboembolism, should primarily be managed according to established cardiovascular principles.⁵

For suspected ICI-associated myocarditis, ICI therapy should be withheld while diagnostic evaluation is undertaken, and patients with clinically significant disease should be admitted for cardiovascular monitoring.⁵ Hemodynamic instability, ventricular arrhythmias, high-grade atrioventricular block, progressive ventricular dysfunction, or rapidly increasing troponin concentrations indicate severe disease and warrant intensive cardiac monitoring and multidisciplinary management. Conventional supportive measures, including temporary pacing, mechanical circulatory support, and guideline-directed heart failure or arrhythmia therapy, should be implemented when clinically indicated.

High-dose corticosteroids remain the cornerstone of initial immunosuppressive treatment. Importantly, observational data suggest that both the timing and intensity of corticosteroid administration influence outcomes. In the multicenter study by Zhang et al., initiation of corticosteroids within 24 hours of presentation was associated with fewer major adverse cardiovascular events than later administration, and higher initial corticosteroid doses were also associated with improved outcomes.¹⁷ Consequently, current expert recommendations favor prompt administration of high-dose intravenous methylprednisolone in patients with definite or strongly suspected clinically significant ICI myocarditis rather than delaying therapy until all diagnostic investigations have been completed.^{5,25} After clinical stabilization and a consistent decline in cardiac biomarkers, corticosteroids are generally transitioned to an oral regimen followed by a gradual taper. The optimal duration of tapering remains uncertain and should be individualized according to clinical status, ventricular function, electrical stability, biomarker trajectory, and concomitant irAEs.

A clinically important subgroup demonstrates an inadequate response to corticosteroids. Steroid-refractory myocarditis should be suspected when myocardial injury, electrical instability, ventricular dysfunction, or hemodynamic compromise persists or progresses despite appropriate initial corticosteroid therapy. Several additional immunosuppressive approaches have been used, including mycophenolate mofetil, intravenous immunoglobulin, antithymocyte globulin, plasma exchange, tacrolimus, alemtuzumab, and targeted immunomodulatory agents.²⁵ However, comparative evidence is extremely limited, and no universally accepted second-line regimen has been established.

Abatacept has emerged as one of the most mechanistically attractive targeted therapies for severe ICI-associated myocarditis. As a CTLA-4 fusion protein, abatacept inhibits CD28-mediated T-cell costimulation and therefore counteracts a central pathway involved in ICI-driven T-cell activation. A proof-of-concept report demonstrated recovery from fulminant, corticosteroid-refractory ICI myocarditis using pharmacodynamically guided high-dose abatacept combined with ruxolitinib and corticosteroids.²⁶ Ruxolitinib, a Janus kinase inhibitor, may provide complementary suppression of cytokine-dependent immune activation. Subsequent clinical experience has supported further investigation of this strategy, particularly in severe disease; nevertheless, the evidence remains insufficient to establish abatacept-ruxolitinib as a universal standard of care.^{5,25,26}

Selection of rescue immunosuppression also requires attention to cardiovascular safety. Infliximab has occasionally been used in refractory cases, but its role is controversial. In a retrospective cohort of patients with ICI myocarditis requiring intensified

immunosuppression, infliximab exposure was associated with higher cardiovascular mortality.²⁷ In addition, TNF- α inhibition carries established concerns in patients with moderate-to-severe heart failure. Therefore, infliximab should generally be avoided in patients with significant ventricular dysfunction or acute heart failure, particularly when alternative immunosuppressive strategies are available.^{25,27} The available evidence does not permit direct comparison of most second-line agents, reinforcing the need for individualized treatment in experienced cardio-oncology centers.

Management of non-myocarditis cardiovascular toxicities differs substantially. Acute coronary syndromes should receive standard evidence-based treatment, including coronary angiography and revascularization when indicated, while simultaneously considering

whether ICI-related vascular inflammation or concomitant myocarditis may be present. Heart failure without evidence of active myocarditis should be treated with guideline-directed heart failure therapy, and arrhythmias should be managed according to their specific mechanism and clinical consequences. Pericardial tamponade requires urgent drainage, whereas suspected immune-mediated pericarditis may additionally require anti-inflammatory or immunosuppressive treatment. Venous thromboembolism should generally be treated according to established cancer-associated thrombosis recommendations rather than with immunosuppression unless a distinct immune-mediated vascular process is demonstrated.⁵ The principal management strategies and considerations for ICI interruption and rechallenge according to cardiovascular toxicity phenotype are summarized in Table 3.

Table 3 Management and ICI rechallenge according to cardiovascular toxicity

Cardiovascular toxicity	Main treatment	ICI management / rechallenge
Myocarditis	High-dose corticosteroids $\pm$ additional immunosuppression	Hold ICI; rechallenge only in highly selected cases
Fulminant myocarditis	IV corticosteroids, intensive support $\pm$ additional immunosuppression	Discontinue; rechallenge generally avoided
ACS	Standard ACS therapy $\pm$ revascularization	Consider resumption after stabilization
Pericardial disease	NSAIDs/colchicine $\pm$ corticosteroids; drainage if needed	Rechallenge after resolution may be considered
Arrhythmias	Rhythm-specific treatment	Depends on underlying mechanism
LV dysfunction / HF	Guideline-directed HF therapy	Individualized after stabilization
Takotsubo syndrome	Supportive/HF therapy	Consider after LV recovery
VTE / arterial thrombosis	Anticoagulation or standard vascular therapy	ICI often can continue/resume
Vasculitis	Corticosteroids $\pm$ additional immunosuppression	Individualized according to severity

Abbreviations: ACS, acute coronary syndrome; HF, heart failure; ICI, immune checkpoint inhibitor; IV, intravenous; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs; VTE, venous thromboembolism. (**Note:** ICI interruption and rechallenge should be individualized according to toxicity severity, cardiovascular recovery, oncological benefit, and multidisciplinary assessment).

The ICI rechallenge dilemma

Whether ICI therapy can be restarted after cardiovascular toxicity is one of the most difficult decisions in contemporary cardio-oncology. The question is particularly relevant because permanent ICI discontinuation may compromise cancer control in patients who have limited alternative therapeutic options. Conversely, re-exposure after a severe cardiovascular irAE may result in recurrent or potentially fatal toxicity. The evidence supporting either strategy remains limited and is derived largely from retrospective series and selected case reports rather than prospective trials.^{5,28}

Historically, ICI-associated myocarditis—particularly severe myocarditis—has generally led to permanent discontinuation of checkpoint inhibition. However, this approach is increasingly being reconsidered in selected patients because myocarditis represents a heterogeneous syndrome, ranging from isolated biomarker abnormalities to fulminant inflammatory myocardial injury. Recent literature has therefore shifted from considering rechallenge an absolute binary decision toward individualized assessment based on the initial severity of myocarditis, degree of recovery, oncological necessity, availability of alternative therapies, and estimated risk of recurrence.²⁸

Before rechallenge is considered, cardiovascular toxicity should have resolved or stabilized to the greatest extent possible. Clinical symptoms, ECG abnormalities, ventricular function, and cardiac biomarkers should be reassessed, with additional imaging when appropriate. The initial cardiovascular phenotype is critical: rechallenge after fulminant myocarditis with cardiogenic shock,

malignant ventricular arrhythmias, or advanced conduction disease carries fundamentally different implications from rechallenge after a mild and rapidly resolving event. Similarly, the expected oncological benefit should be substantial enough to justify the cardiovascular uncertainty.

If rechallenge is undertaken, the decision should be made jointly by oncology and cardio-oncology specialists and accompanied by intensified cardiovascular surveillance. Strategies may include avoiding the original combination ICI regimen, using monotherapy when oncologically acceptable, obtaining baseline ECG and cardiac biomarkers before re-exposure, and performing serial assessment during the early treatment cycles.^{5,28} There is currently no validated prophylactic immunosuppressive regimen that reliably prevents recurrent myocarditis, and routine preventive immunosuppression cannot be recommended.

Rechallenge decisions following non-myocarditis cardiovascular events may be less restrictive. An acute coronary syndrome successfully treated with revascularization, controlled arrhythmia, resolved pericarditis, or adequately treated venous thromboembolism does not necessarily mandate permanent ICI discontinuation. In these situations, the probability that the event represents a direct immune-mediated toxicity, the likelihood of recurrence, cardiovascular stability, and the expected oncological benefit should determine whether therapy can safely continue or resume.⁵

Ultimately, management of ICI-associated cardiovascular toxicity should avoid two extremes: undertreatment of potentially fatal immune-mediated disease and unnecessary permanent withdrawal of effective anticancer therapy for cardiovascular events that may be

manageable or unrelated to direct immune toxicity. A phenotype- and severity-based multidisciplinary approach offers the most rational framework while prospective evidence remains limited.

Emerging concepts and future directions

Despite increasing recognition of ICI-associated cardiovascular toxicity, the ability to predict which patients will develop clinically significant events remains limited. Current cardiovascular assessment primarily identifies pre-existing cardiovascular disease and treatment-related risk factors, but these variables alone cannot adequately predict immune-mediated toxicity. Future cardio-oncology strategies will therefore need to integrate conventional cardiovascular risk assessment with immunological, molecular, and imaging biomarkers that reflect individual susceptibility to checkpoint inhibition.^{5,29}

One of the major unmet needs is the identification of reliable predictive biomarkers. Cardiac troponins are central to the detection of myocardial injury once it has occurred, but their role as pretreatment predictors of toxicity is considerably less established. Moreover, troponin elevation lacks etiological specificity and may occur in acute coronary syndromes, pulmonary embolism, renal dysfunction, sepsis, tachyarrhythmias, and concomitant skeletal muscle inflammatory syndromes. Combining cardiac biomarkers with non-cardiac markers of immune-mediated injury may improve diagnostic and prognostic assessment. Creatine phosphokinase, inflammatory indices, and other circulating markers have therefore been investigated, particularly because myocarditis frequently overlaps with myositis.³⁰ Nevertheless, no circulating biomarker or biomarker panel has yet demonstrated sufficient prospective performance to reliably predict ICI-associated myocarditis before treatment.

Emerging molecular biomarkers may provide greater biological specificity. Circulating cytokines, immune-cell phenotypes, autoantibodies, microRNAs, and T-cell receptor characteristics are being investigated as potential indicators of susceptibility to cardiovascular irAEs. MicroRNAs are of particular interest because of their tissue-specific expression and potential ability to reflect myocardial immune injury. However, most candidate biomarkers have been evaluated in small or heterogeneous cohorts, and external validation remains limited. Importantly, biomarkers developed for prediction of general irAEs cannot automatically be assumed to predict cardiovascular toxicity, which is substantially less common and may have distinct immunological determinants.³¹

Genetic and hematopoietic factors represent another emerging area. Clonal hematopoiesis of indeterminate potential may provide a mechanistic connection among aging, malignancy, systemic inflammation, and cardiovascular disease. The prospective association between CHIP and ICI-associated myocarditis reported in a cardio-oncology cohort suggests that pre-existing clonal alterations in hematopoiesis may modify susceptibility to cardiovascular immune toxicity.¹¹ However, this observation requires validation in larger and more diverse cohorts before CHIP sequencing can be incorporated into routine cardiovascular risk stratification. More broadly, integration of germline genetics, somatic mutations, transcriptomics, proteomics, metabolomics, and immune profiling may eventually permit identification of biological signatures that distinguish patients susceptible to cardiac toxicity from those who can receive ICI therapy with relatively low cardiovascular risk.

Advanced cardiovascular imaging may also contribute to earlier and more precise phenotyping. Conventional echocardiographic LVEF is insufficiently sensitive to exclude ICI myocarditis, while CMR findings can be nondiagnostic, particularly early in the disease

course.¹⁴ Quantitative myocardial strain, parametric CMR mapping, and molecular or metabolic imaging may improve detection of subclinical cardiovascular injury. Equally important, imaging research should extend beyond the myocardium. Serial vascular imaging could clarify whether ICI-associated acceleration of atherosclerosis represents a transient inflammatory response or a persistent modification of plaque biology after treatment discontinuation. Such studies may also help identify patients who could benefit from intensified preventive cardiovascular therapy.

Artificial intelligence offers a potential framework for integrating these increasingly complex data. Machine-learning models could theoretically combine baseline clinical characteristics, cancer type and stage, ICI regimen, ECG features, longitudinal biomarker measurements, echocardiographic parameters, CMR findings, and molecular data to generate individualized estimates of cardiovascular risk. However, AI-based prediction of ICI cardiovascular toxicity remains an investigational concept rather than a clinically validated strategy. The rarity of severe cardiovascular irAEs, inconsistent diagnostic definitions, missing longitudinal data, and substantial heterogeneity among cancer populations create major challenges for model development. Large multicenter datasets with adjudicated cardiovascular outcomes will be necessary before such approaches can be considered clinically reliable.

Another priority is improved characterization of the relationship between inflammatory and non-inflammatory cardiovascular phenotypes. Current evidence increasingly suggests that ICI-associated cardiovascular toxicity may be better conceptualized as an inflammatory continuum rather than a collection of completely independent complications.³² At one end are acute, overt immune-mediated syndromes such as fulminant myocarditis, while less dramatic immune activation may contribute to endothelial dysfunction, ventricular dysfunction, and acceleration of atherosclerosis.^{4,32} Determining whether these manifestations share common biological pathways could have important implications for both surveillance and treatment.

Sirtuin 1 (SIRT1), an NAD⁺-dependent deacetylase involved in the regulation of oxidative stress, inflammation, endothelial function, and cellular metabolism, has emerged as a potential molecular target in cardiovascular disease.³³ Given the contribution of inflammatory and endothelial pathways to ICI-associated cardiovascular toxicity,⁵ SIRT1 may represent a potential mechanistic link and an exploratory biomarker or therapeutic target in this setting. However, direct clinical evidence linking circulating SIRT1 levels or pharmacological SIRT1 modulation to the prediction, prevention, or treatment of ICI-associated cardiotoxicity is currently lacking. Therefore, the potential role of SIRT1 in ICI-associated cardiovascular toxicity requires dedicated mechanistic and prospective clinical investigation.

Finally, the field requires prospective evidence rather than continued reliance on pharmacovigilance databases, retrospective registries, and case series. Standardized definitions of cardiovascular events, systematic baseline assessment, longitudinal biomarker collection, and predefined imaging protocols should be incorporated into future oncology trials and dedicated cardio-oncology registries. Prospective studies should determine whether biomarker surveillance improves clinical outcomes, whether cardiovascular risk-factor optimization can reduce ICI-associated atherosclerotic events, and which immunosuppressive strategies provide the best balance between control of cardiovascular toxicity and preservation of antitumor immunity. Ultimately, precision cardio-oncology in the ICI era will depend not simply on detecting toxicity earlier, but on identifying the individual patient in whom clinically meaningful cardiovascular

toxicity is likely to occur and tailoring surveillance and prevention accordingly.

Conclusions

The cardiovascular consequences of immune checkpoint inhibition extend well beyond myocarditis. Although ICI-associated myocarditis remains the most recognized and potentially life-threatening cardiovascular irAE, increasing evidence demonstrates a broader spectrum that includes accelerated atherosclerosis and acute ischemic events, pericardial disease, arrhythmias and conduction disturbances, heart failure and non-inflammatory ventricular dysfunction, as well as vascular and thromboembolic complications.⁵ These manifestations are unlikely to reflect a single pathophysiological process. Rather, checkpoint inhibition may disrupt myocardial immune tolerance, amplify vascular inflammation, and destabilize pre-existing cardiovascular disease, producing clinically distinct phenotypes across susceptible patients.^{4,29}

This broader perspective has important implications for clinical practice. Cardiovascular assessment of patients receiving ICIs should not focus exclusively on early detection of myocarditis. Baseline characterization of cardiovascular disease and modifiable risk factors, vigilance for new cardiovascular symptoms, and phenotype-directed use of biomarkers and multimodality imaging are necessary to recognize the full spectrum of toxicity. At the same time, cardiovascular events occurring during ICI therapy should not automatically be attributed to immune-mediated toxicity, particularly in patients with cancer who frequently have competing cardiovascular and thrombotic risk factors.

Management requires a balance between cardiovascular safety and preservation of effective anticancer therapy. Prompt ICI interruption and immunosuppression remain essential for clinically significant myocarditis, whereas many non-myocarditis complications should primarily be treated according to established cardiovascular principles. Decisions regarding ICI discontinuation or rechallenge should therefore consider the cardiovascular phenotype and severity, degree of recovery, probability of treatment-related causality, oncological benefit, and availability of alternative cancer therapies.⁵

Future progress will depend on prospective studies capable of defining reliable predictors of cardiovascular toxicity, validating risk-based surveillance strategies, and determining the optimal management of both inflammatory and non-inflammatory cardiovascular complications. Integration of molecular biomarkers, immune profiling, advanced imaging, and potentially multi-omics approaches may ultimately enable more individualized risk assessment. Until such evidence becomes available, close collaboration between oncology and cardiology remains central to recognizing cardiovascular toxicity early while avoiding unnecessary interruption of potentially life-prolonging immunotherapy.

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All of the authors contributed planning, conduct, and reporting of the work. All authors contributed to the conception, literature review, drafting, and critical revision of the manuscript and approved the final version

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